ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Sickle Cell Disease: New Treatments and Their Rationale

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H&O What have been the biggest changes in the management of sickle cell disease over the past 2 decades?

JF Implementation of newborn screening and penicillin prophylaxis for children with sickle cell disease were significant advances in the 1980s. Thereafter, I would point to hydroxyurea and the increased use of blood transfusions as the changes that have made the greatest impact.

Hydroxyurea inhibits the formation of sickle erythrocytes by increasing levels of fetal hemoglobin. The major study by Charache and colleagues about the use of hydroxyurea in sickle cell disease came out in the *New England Journal of Medicine* in 1995. The data showed that for adults with severe sickle cell anemia—those who were having at least 3 painful crises a year—hydroxyurea reduced the number of painful crises, episodes of acute chest syndrome, and the need for blood transfusions.

Since then, clinicians have been trying to figure out who will benefit from this drug beyond the most severe patients. Many of us have broadened out the use of hydroxyurea to nearly all of our patients with sickle cell disease, regardless of genotype or severity of disease.

The other big advance relates to the use of hydroxyurea in children. Data from BABY HUG (The Pediatric Hydroxyurea Phase 3 Clinical Trial), which was published in the *Lancet* in 2011 and *Blood* in 2012, suggested that very young children can benefit from hydroxyurea. As a result, it has become more commonplace to treat even very young children—those younger than 18 months—with hydroxyurea.

We used to wait until people with sickle cell disease became ill, and then we managed the complications. Now we are taking a more preemptive approach; we start hydroxyurea before the patient develops chronic complications of sickle cell disease, such as chronic pain and end organ dysfunction.

Another change is that it has become more commonplace to give blood transfusions to patients with sickle cell disease. Data from Drasar and colleagues published in the *British Journal of Haematology* in 2011 show that in adults with sickle cell disease, most of the increase in blood usage is from scheduled, preventative transfusions for a history of stroke, pain, or acute chest syndrome, not from acute transfusions.

H&O Why has the use of prophylactic blood transfusions increased?

JF The reason for that is multifactorial. The main indication for prophylactic blood transfusion in this population is secondary stroke prophylaxis. We know that if an individual with sickle cell disease has a stroke, the risk of having another stroke in the next few years is greater than 50%. Starting a regimen of regular blood transfusions—approximately 1 per month—to decrease hemoglobin S percentage can greatly diminish the risk of having a second stroke.

Something we do not have much data on is whether blood transfusions can be used for people with severe sickle cell disease, such as those who are having painful vaso-occlusive crises that require frequent hospitalizations, or multiple episodes of acute chest syndrome. Since we have few options for treatment, some of us—including myself—have started to use blood transfusions in these patients, so that is becoming more commonplace.

We have also started to use blood transfusions for primary stroke prevention in children, based on work by Adams and colleagues that was published in the *New England Journal of Medicine* in 1998. This study showed that blood transfusions reduce the risk of stroke in children who have abnormal results on transcranial Doppler ultrasonography.

H&O What are the other reasons the use of blood transfusion has increased?

JF One reason is that many large medical centers are providing better-matched blood, allowing us to perform safer transfusions. Dr Elliott Vichinsky of the Children's Hospital Oakland Research Institute in California led this charge some time ago. In a study published in the *New England Journal of Medicine* in 1990, he demonstrated that when patients with sickle cell disease received standard ABO- and Rh-matched blood, there was a high likelihood—approximately a 3% chance per unit—of forming antibodies directed against the donor red blood cells. The main reason for this is that African Americans express red cell antigens at different frequencies than the largely white donors.

What Dr Vichinsky and other researchers have shown is that we can greatly reduce the risk of alloimmunization by going beyond the traditional ABO- and Rh-matching, and match for additional loci: C, E, and Kell. That is why many centers, ours included, make a great effort do this matching. In order to provide optimally matched blood for our patients, however, we need a large African American donor pool. We have been making a big push here in Milwaukee at the BloodCenter of Wisconsin to encourage African Americans to donate blood.

The other change that makes it safer to give blood is the availability of new iron chelators. Patients can accumulate very high levels of iron when we give them blood, which can limit our ability to further transfuse them. Previously, the only option for treatment was deferoxamine (Desferal, Novartis), which has a short half-life and requires a continuous, usually subcutaneous, infusion. This required that the patients insert a needle under their skin every night for an overnight infusion that lasted 8 hours.

As you can imagine, doing that for years on end was cumbersome and adherence was not great. In the past several years, however, 2 new iron chelators have come out in the United States. Deferasirox (Exjade, Novartis), which was approved by the US Food and Drug Administration (FDA) in 2005, is a tablet that dissolves in liquid. The patient mixes it up into a slurry and drinks it once a day. Deferiprone (Ferriprox, ApoPharma), which the FDA approved in 2011, comes in capsule form and is taken orally 3 times a day.

Because both of these options are much easier than struggling with a subcutaneous infusion, they have made it easier for clinicians to manage iron overload and recommend a chronic transfusion program for patients. With better-matched blood and the availability of new iron chelators, we can tell patients that the chance of developing an antibody to the transfused blood is smaller, and that excess levels of iron can be managed more effectively.

H&O What are some of the newest treatments for sickle cell disease?

JF Many different approaches are being studied, so I will start with the 2 trials I am involved with. First, a team led by Dr David Nathan and myself are investigating the use of the adenosine A_{2A} receptor agonist regadenoson in treating painful crises in sickle cell disease. This agent is already approved as a pharmacologic stress agent in radionuclide myocardial perfusion imaging. Regadenoson targets the adenosine A_{2A} receptor and causes coronary vasodilatation when given at high bolus doses. We have found that a low-dose infusion of the drug provides an anti-inflammatory effect without any of the cardiovascular toxicity. We published our phase 1 results in *Blood* in 2013. We were able to use a low-dose infusion of this drug to inhibit the activation of invariant natural killer T (iNKT) cells. This study was an extension of the work done by Dr Joel Linden, who was able to demonstrate that iNKT cells greatly impacted inflammation and tissue injury in a mouse model of sickle cell disease. We are currently initiating a phase 2, placebo-controlled, multicenter trial of regadenoson in painful crises that is funded by the National Heart, Lung, and Blood Institute.

The other agent we are investigating is the monoclonal antibody NKTT120, which is being developed by NKT Therapeutics. This agent specifically depletes iNKT cells and has the potential to prevent the inflammation that promotes vaso-occlusive crises. We are currently conducting a phase 1 safety and dose-escalation trial.

Another agent that is being evaluated in the setting of an acute vaso-occlusive crisis is the pan-selectin inhibitor GMI-1070, which is being developed by GlycoMimetics. An ongoing randomized phase 2 trial is evaluating the effects of GMI-1070 on the course of vaso-occlusive crises. In a press release in early 2013, the company announced that patients treated with GMI-

1070 experienced a reduction in the duration of vaso-occlusive crises, hospital stay, and the use of opioids.

There are also agents in development that stimulate fetal hemoglobin production, similar to hydroxyurea. Dr Abdullah Kutlar of Georgia Regents University is studying the agent pomalidomide (Pomalyst, Celgene), and Dr Maureen Okam at Dana-Farber Cancer Institute is looking at another agent to increase fetal hemoglobin: the histone deacetylase inhibitor vorinostat (Zolinza, Merck). Both agents might be useful in conjunction with hydroxyurea, and may produce a synergistic effect on fetal hemoglobin production.

The other strategy that is being investigated in sickle cell disease is new approaches to stem cell transplantation. The first challenge is finding appropriate donors, which is especially difficult in a minority population. The other problem is that traditional myeloablative stem cell transplants were causing excessive amounts of toxicity and a fairly high rate of mortality in adults. A number of advances have been made in this area, such as nonmyeloablative transplants using reduced-intensity conditioning regimens. In nonmyeloablative approaches, the goal is to achieve stable chimerism, a mix of patient and donor hematopoiesis that improves the manifestations of sickle cell disease, but often does not cure the patient. The important study on reduced-intensity conditioning regimens, which came out in 2009 in the *New England Journal of Medicine,* found that 9 out of 10 patients—the ones who were able to find a match—achieved long-term engraftment with stable mixed chimerism and improvement of their sickle cell-related symptoms.

The other new approach to stem cell transplant is performing a haploidentical transplant, which overcomes the problem of a lack of matched donors. Instead of looking for a match from an unrelated donor, we look for a half match from a parent. A group from Johns Hopkins University did this type of nonmyeloablative transplant in 14 patients, including 12 adults. About half of the patients achieved a high level of peripheral blood chimerism; that is, they went from S or S+C percentages nearing 100% to less than 50%. In some cases, the patient had no detectable hemoglobin S if the donor did not have the sickle cell trait.

The limitation of haploidentical transplants is that approximately half of the patients will have graft failure. Since there is less toxicity with this and other nonmyeloablative approaches, however, most patients with graft failure will simply revert back to their prior disease state. A 50% chance to markedly improve the disease or cure it in some cases may be worth the small risk of toxicity associated with a nonmyeloablative transplant.

We often recommend stem cell transplants for children with sickle cell disease, especially in those with hemoglobin SS, if they have a matched sibling. There are differing schools of thought as to which children are the most appropriate candidates. Some advocate reserving transplantation for children who have had severe complications. On the other hand, many patients will develop complications over time that will lead to end organ disease. Delaying the procedure in these cases may increase the risk of future transplants.

I consider adults to be candidates for transplantation if they have serious complications from sickle cell disease, including stroke, vasculopathy, severe episodes of acute chest syndrome, and painful vaso-occlusive crises. Transplantation is not considered part of standard care for adults, however, and is generally done as part of a trial. Finding a matched donor is difficult, and the cost of the procedure is high—approximately $400,000. On the other hand, the cost of treating the disease adds up over time.

H&O How do the anti–cell adhesion agents work?

JF GMI-1070 works by blocking the selectins, which are molecules that help red blood cells and other cells involved in vaso-occlusion adhere to the vascular endothelium. The idea is to improve vaso-occlusion by blocking the selectins.

GMI-1070 and regadenoson are being developed to deal with acute crises. Treating acute crises may be more challenging than preventing them. By the time a vaso-occlusive crisis has started, you are dealing with a florid process and, pertinent to regadenoson, extreme amounts of inflammation. Although there is value to treating and improving the course of acute crises, preventing them altogether would be preferable.

H&O What are some of the disadvantages of hydroxyurea?

JF The big disadvantage of hydroxyurea is that patients need to remember to take it every day. The most worrisome side effect is diminished blood cell counts, which increase the risk of infection and bleeding, so we monitor the blood cell count each month. The challenge is to find the dose that provides the maximal production of fetal hemoglobin without causing an excessive degree of myelosuppression.

I tell my patients that this drug is important to take because it will reduce the number of sickle cells they have and this will decrease pain and acute chest events. In addition, 3 studies have demonstrated that it improves survival. Remembering to take a pill every day is a small price to pay for such important benefits.

H&O Do you think that hydroxyurea is underused?

JF Yes, and this is a big problem. According to a National Institutes of Health consensus statement, there are several barriers to use of the drug. First, patients do not

always take their hydroxyurea, either because they forget or because they have concerns about toxicity. There is a theoretical risk of leukemia, but an increase in risk has never been shown to occur in the 20 years we have been using this drug. The other big barrier to hydroxyurea is that healthcare providers are not prescribing it often enough. A major reason for that is that few healthcare providers specialize in treating sickle cell disease. Much of the care falls to primary care physicians, who may not have a lot of training in sickle cell disease and may not feel comfortable prescribing a drug like hydroxyurea.

H&O What other approaches are being studied for use in sickle cell disease?

JF Many investigators are evaluating gene therapy strategies to cure patients of sickle cell disease. Different approaches include using lentivirus vectors to transfer the β-globin gene into hematopoietic stem cells vs replacing the gene using induced pluripotent stem cells. The latter approach, pioneered by Dr Tim Townes of the University of Alabama, overcomes the problem of insertional mutagenesis with lentivirus vectors. The mutated β-globin gene is replaced with a functional copy in pluripotent stem cells, which are then differentiated to hematopoietic cells and transplanted into sickle mice. Although this approach has corrected the sickle cell phenotype in mice, it is not ready for use in humans.

There have been 2 notable studies in the area of nitric oxide that unfortunately did not have positive findings. Nitric oxide is a vasodilator that can inhibit platelet function, among many other actions, and it is known to be depleted in patients with sickle cell disease. Increasing levels of nitric oxide could relax constricted blood vessels, improve blood flow, and potentially benefit patients with sickle cell disease. In a randomized, placebo-controlled trial, the effects of inhaled nitric oxide were examined during vaso-occlusive crises in 150 participants. Although smaller studies had suggested benefit from inhaled nitric oxide, there was no difference in resolution in crisis between the inhaled nitric oxide and placebo group in this definitive study. Another trial in the field of nitric oxide was the walk-PHaSST (Treatment of Pulmonary Hypertension and Sickle Cell Disease With Sildenafil Treatment) trial, which evaluated sildenafil, a phosphodiesterase-5 inhibitor, in patients with sickle cell disease and pulmonary hypertension. This trial was led by Dr Mark Gladwin, and had Dr Roberto Machado as the first author. Unfortunately, this study had to be stopped owing to an increased number of vaso-occlusive crises in the sildenafil arm. Nitric oxide has important roles in pain nociception and increasing levels with sildenafil may have contributed to this unexpected complication.

Many other therapies are also in the early stages of development—probably a list of 20 or 30. Because hydroxyurea is currently the only FDA-approved therapy for patients with sickle cell disease, it is very nice to see so many therapies being examined. Hopefully, many of these new approaches will be shown to be beneficial and can be incorporated into the clinic.

Suggested Readings

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